REMARKS

I. Preliminary Remarks

The Applicants thank SPE Gary Knunz and Examiner Nichols for granting a telephonic interview to the Applicant's attorney David A. Gass and the undersigned agent on December 22, 2003.

Claims 1-154 have been canceled without prejudice. Claim 151 is pending in U.S. Application No. 09/548,368 and claims 152-153 are pending in U.S. Application No. 09/794,925. Prosecution in these applications have progressed further than prosecution in the present application, therefore these claims have been canceled by the foregoing amendment. Claims 157-158 have been allowed in U.S. Application No. 09/548,366 and therefore have been canceled by the foregoing amendment.

The first paragraph of the specification was amended to clarify the priority claim as discussed with the Examiners during the telephonic interview. This application is a continuation of U.S. Application No. 09/416,901 filed October 13, 1999, which is a continuation-in-part of both U.S. Application No. 09/414,133 filed September 23, 1999 and PCT Application No. PCT/US99/20881, which both claim priority benefit of U.S. Provisional Application No. 60/101,594 filed September 23, 1998. Therefore, the present application has an effective filing date of September 23, 1998.

The sequences set out as SEQ ID NO: 3 and 4 in the substitute sequence listing, filed on December 30, 2002, are not identical to the sequences set out in Figure 3 as filed. Therefore, the attached substitute sequence listing is submitted to revise the sequences of SEQ ID NOS: 3 and 4 so that they are identical to the sequences shown in Figure 3 as filed. These amendments do not introduce new matter, but address an internal inconsistency.

In paragraph 7 of the Action, the Examiner asserted that the declaration filed on June 27, 2001 was defective because it incorrectly claims priority to Provisional Application Nos. 60/101,594 and 60/155,493. As described above, and during the telephonic interview, this priority claim is correct according to 35 U.S.C. § 365 (c) which states an international application designating the United States shall be entitled to the benefit of the filing date of a prior application. MPEP §1983.03(c) further explains that a U.S. national stage application submitted under 35 U.S.C. § 371 may include a claim under 35 U.S.C.

§§ 119(a) and 365(b), 35 U.S.C. §§119(e), or 35 U.S.C. §§ 120 and 365(c) for benefit of the filing date of a prior application or applications. The present application is designated as a continuation of a prior U.S. regular application that was pending at the time the present application was filed. The parent application, in turn, claims proper priority to both provisional applications.

This application properly claims priority to U.S. Application No. 09/416,901 as a continuation application. A new declaration does not need to be signed for a continuation or divisional application if all inventors are the same and no new matter is added pursuant to 37 C.F.R. § 1.63(d)(1). Thus, a new declaration is not needed in view of the copy of the declaration from the parent application that was previously filed.

II. Restriction

In paragraph 2 of the Action, the Examiner stated that new claims 170-200 are directed to an invention that is independent or distinct from the originally claimed invention. As discussed in the telephonic interview, claims 189-192 and 200 are directed to isolated nucleic acid molecules that encode a biologically active human aspartyl protease having a valine at position 130 of SEQ ID NO: 4 or a conservative substitution therefor wherein the nucleotide sequence either hybridizes to a specified sequence such as the complement of SEQ ID NO: 3, or is identical across its length to SEQ ID NO: 3, *e.g.*, a sequence set forth in SEQ ID NO: 3. Dependent claims 193-194 are directed to related vector and host cell subject matter. Claims 195-199 are directed to isolated biologically active human aspartyl proteases containing a valine at position 130 of SEQ ID NO: 4 or a conservative substitution therefor that is similarly defined with respect to SEQ ID NO: 4 or polynucleotides that encode the polypeptide.

It was agreed in the telephonic interview that claims 189-200 relate to the elected subject matter of the polynucleotide sequence of SEQ ID NO: 3 and the polypeptide sequence of SEQ ID NO: 4. As explained in the preceding paragraphs, claims 189-200 embrace the elected subject matter. Therefore, if the pending claims are considered to be in novel and non-obvious, the Examiner will consider adding claims 189-200 back into the present application.

Powell *et al.* EPO855444 ('444) and U.S. 6,319,689 (hereinafter Powell '444) disclosed a polypeptide with 99.6% similarity to SEQ ID NO: 4. In particular, the amino acid sequence in '444 has a Glu at position 130, while SEQ ID NO: 4 has a Val at position 130. A substitution of Val for Glu is not a conservative substitution, as Glu is an acidic residue and Val is an aliphatic residue. The amino acid substitutions in the claimed polypeptides, relative to wildtype Asp2 sequence in SEQ ID NO: 4, must be conservative substitutions. Thus, the claims do not read on the polypeptide disclosed in '444, as the difference in the '444 sequence at position 130 is not a conservative substitution. For these reasons, the protein disclosed in Powell '444 is not within the scope of the claims 189-200.

Claims 170-188 are directed to methods of identifying agents that inhibit or modulate the aspartyl protease activity of the polypeptide encoded by the polynucleotides of claims 155-156. The Applicants request that if the product claims 155-156 are found novel and non-obvious under 35 U.S.C. § 103(a), methods of using the product (claims 170-188) be rejoined. *See* 1184 OG 86, (1996).

III. Declaration of Michael Bienkowski, Ph.D.

In paragraph 5 of the Action, the Examiner stated the Applicants' Declaration of Michael Bienkowski, Ph.D. has been entered but not considered because "no rejections have been set forth in the instant Application and the Applicant has not put forth any reason for the Declaration to be filed." In actuality, the Examiner now raised rejections and questioned the priority claim and cited Applicants own related application as alleged prior art. Consideration of the declaration is requested.

IV. Information Disclosure Statement

In paragraph 6 of the Action, the Examiner stated the information disclosure statement filed on June 19, 2003 failed to comply with 37 C.F.R. § 1.98 (a)(2), as legible copies of cited U.S. patents and publications were not submitted with the statement. The applications listed on this IDS were to inform the Examiner of related pending applications, all of which are available at the PTO. None of the applications are "U.S. Patents." The Applicants do not intend to provide copies of all listed pending related applications, which are substantially identical in the specification of the present application. Copies of pending claims can be provided at the Examiner's request.

V. The Double Patenting Rejection should be Withdrawn

In paragraph 8 of the Action, the Examiner provisionally rejected claims 151, 155, 161 and 162 under the judicially created doctrine of obviousness-type double patenting over claims 1, 3, 21 and 22 of copending Application No. 09/795,847. In the foregoing amendment, claims 151 and 161-162 have been canceled. The Applicants have received a Notice of Allowance in '847, in which claims 45, 46, 52-60 and 63-68 are in condition for allowance. Submitted herewith is a terminal disclaimer to overcome this double patenting rejection. Accordingly, the Applicants request that the obviousness-type double patenting rejection be withdrawn in the present application.

In paragraph 9 of the Action, the Examiner also provisionally rejected claim 151 under the judicially created doctrine of obviousness-type double patenting over claim 1 of copending Application No. 09/794,743. In the foregoing amendment, claim 151 has been canceled. Therefore, this rejection has been rendered moot and the Applicants request that the obviousness-type double patenting rejection be withdrawn in the present application.

VI. The Rejection under 35 U.S.C. § 112, First Paragraph should be Withdrawn.

A. The Claims are Enabled by the Specification.

In paragraph 10 of the Action, the Examiner rejected claims 151-169 under 35 U.S.C. § 112, first paragraph for lacking enablement. In particular, the Examiner stated the specification does not reasonably provide enablement for polypeptides that are at least 95% identical to a fragment of SEQ ID NO: 4 or polypeptides that hybridize to the complement of SEQ ID NO: 3 and fragments thereof. Claims 151-154 and 157-158 have been canceled without prejudice. The Applicants traverse this rejection as it pertains to claims 155 -156 and 159-169.

The Examiner stated "the specification fails to provide guidance for the successful isolation, cloning and expression of fragments, derivatives and variants of SEQ ID NO: 3 and SEQ ID NO: 4." The specification describes how to make fragments of SEQ ID NO: 4 with the transmembrane domain deleted. In addition, Example 8 (pages 63-68) demonstrates that the transmembrane deleted fragments are active. In addition, the specification teaches that the polypeptide of SEQ ID NO: 4 has a pre-propeptide that spans residues 22-45 and a propeptide that spans residues 46-57. (See page 21, lines 1-5). One of

skill in the art understands that these peptide may be deleted to create an active fragment. The specification also teaches assays for measuring the aspartyl protease activity of the fragments. For example, a novel cell line for measuring processing of APP into amyloid beta is taught at page 42, lines 19-21. These cells can be transfected with a polynucleotide that expresses the claimed fragment. At page 53, lines 20-29, the Applicants teach human cell lines that process APP which provide a means for screening for APP processing activity. Production of amyloid beta peptide in culture can be measured by EIA as described at pages 56-57. Example 12 (pages 80-82), provides cell-free assays using synthetic peptide subtrates to measure the aspartyl protease activity of the fragments.

The specification adequately enables polynucleotides which encode polypeptide fragments that are 95% identical to the amino acid sequence of SEQ ID NO: 4. The Applicants disclosed two amino acid sequences (SEQ ID NOS: 6 and 8) which are at least 95% identical to the amino acid sequence of SEQ ID NO: 4. Example 12 (pages. 80-82) demonstrates that, in addition to having 95% identity to SEQ ID NO: 4, the Asp2 polypeptide of SEQ ID NO: 6 possesses APP processing activity similar to Asp2 polypeptide of SEQ ID NO: 4. The Applicants also disclosed the amino acid sequence of murine Asp2 as SEQ ID NO: 8, which is greater than 95% identical to SEQ ID NO: 4. Example 3 (pages 50-51) is a working example which enables one of skill in the art to isolate polynucleotides which encode Asp2 polypeptides having 95% identity to SEQ ID NO: 4 from a cDNA library.

The Examiner also asserts that the Applicants has provided little or no guidance to determine which positions within the protein can tolerate change (*e.g.* such as by amino acid substitutions or deletions.) The structural components necessary for aspartyl protease activity are taught in the specification, and the claimed fragments are required to have the aspartyl protease active site tripeptides DTG and DSG. The specification, at page 26, lines 8-11, teaches that aspartyl proteasesw possess a two domain structure which folds to bring two aspartyl protease residues into proximity of the active site and the active site is embedded in the short tripeptide motifs DTG and DSG. Therefore, small or inactive fragments and variants are not encompassed by the claims. The structural and functional limitations in the claim provide the necessary guidance for one of skill in the art to make and use the polynucleotides and polypeptides of the present invention. Moreover, the assays provided in the application allow one to determine whether any particular variant is active

using only routine screening, and routine screening does not constitute "undue experiment" under the law.

The Examiner cites Tanahashi and Tabira (*Neuroscience Letters*, 307: 9-12, 2001) to demonstrate the unpredictability of the BACE (Asp2) art. This reference provides three novel alternatively spliced isoforms of BACE, and teaches that changes in the amino acid sequence affects protease activity. However, the splice variants disclosed in Tanahashi and Tabira retained the ability to process APP into amyloid beta even though the processing efficiency varied. The present claims require the fragments and variants to retain aspartyl protease activity but do not require a specific efficiency. Therefore, this reference is not effective for demonstrating the unpredictability of the current BACE art, or that undue experimentation is needed to make and use the polynucleotides and polypeptides of the present invention. The additional references cited by the Examiner, in paragraphs 17 and 18 of the Action, do not relate specifically to the sequences of the present invention, and the foregoing remarks demonstrate that undue experimentation is not needed for one of skill in the art to make and use the claimed polynucleotide and polypeptide sequences of the present invention.

B. The Specification Provides Adequate Written Description

In paragraph 20 of the Action, the Examiner rejected claims 151 and 155 under 35 U.S.C. § 112, first paragraph, for allegedly lacking an adequate written description. In particular, the Examiner stated the specification does not provide adequate written description for a genus of polypeptides having at least 95% identity to SEQ ID NO: 4. Claim 151 has been canceled without prejudice; however, the the Applicants traverse this rejection of claim 155.

Claim 155 is directed to a polynucleotide encoding a polypeptide comprising an amino acid sequence that is 95% identical to a continuous fragment of SEQ ID NO: 4. The recited fragment includes the aspartyl protease active site tripeptides, DTG and DSG, and exhibits aspartyl protease activity involved in processing APP into amyloid beta. Also, the encoded polypeptide must exhibit aspartyl protease activity involved in processing APP into amyloid beta.

Polypeptides that are 95% identical to a fragments of SEQ ID NO: 4 are contemplated in the specification at page 8, line 7-9. The recited fragment and the variant polypeptides are structurally and functionally defined in the claim, and these recitations are described throughout the specification. For example, continuous fragments that retain aspartyl protease activity are described at page 19, lines 1-2, and page 31, lines 3-6. Aspartyl protease activity involved in processing APP into amyloid beta is described in the specification at page 2, lines 20-21, page 42, lines 19-21, and pages 59-63 (Example 7). Fragments that include the aspartyl protease active site tripepetides DTG and DSG are described in the specification at page 26, lines 10-12, page 49, lines 7-9, and page 50, lines 11-2.

The structural and functional limitations recited in claim 155 meet the Written Description Guidelines of the United States Patent and Trademark Office, 66 Fed. Reg. 1099 (January 30, 2001). In particular, Example 14 of the Revised Interim Written Description Guidelines Training Materials remains consistent with those guidelines and teaches that a claimed variant polynucleotide that is substantially similar to a sequence taught in the specification, along with a functional limitation that the claimed variant polynucleotide encodes variant polypeptides that exhibit an identified activity, meets the written description requirement if the required activity can be determined as described in the specification. In the instant case, the claimed polynucleotide must encode a polypeptide having a sequence that is at least 95% identical to a structurally and functionally defined fragment of SEQ ID NO: 4, and therefore do not have substantial variation from the sequence of SEQ ID NO: 4, as taught in the specification. The allegation that a requirement for at least 95% identity "does not require that the polypeptide possess any particular conserved structure" is simply incorrect because 95% identity *per se* is highly conserved structure.

C. Conclusion

In view of the foregoing remarks, pending claims 155 and 156 are supported by an adequate written description and are enabled by the specification. Therefore, the Applicants request the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

VII. The Rejection under 35 U.S.C. § 112, Second Paragraph should be Withdrawn.

In paragraph 26 of the Action, the Examiner rejected claims 154, 156, 159, 165, 168 and 169 for being indefinite and failing to particularly point out and distinctly claim the invention. Claim 154 have been canceled without prejudice. The Applicants traverse this rejection in view of claims 156, 159, 165, 168 and 169.

In paragraph 27 of the Action, the Examiner states the term "heterologous" is a relative term which renders claims 159, 168 and 169 indefinite. The term "heterologous" is well known in the art and a recent search of the U.S. Patent and Trademark Office Issued Patent Database identified more than 3000 issued patents that recite the term "heterologous" in the claims. A portion of this search is attached herewith as Appendix A. The specification provides examples of heterologous peptide tags commonly used in the art at page 37, lines 16-20. Similarly, the specification provides a list of promoters derived from a different source than the host cell (see page 36, lines 13-16; and page 39, lines 12-25), as well as a working example describing heterologous expression of the Asp2 polypeptide using a CMV (cytomegalovirus) promoter in COS (mammalian) cells (See Example 11, pages 78-80). A person of ordinary skill has no difficulty determining whether an attached sequence is heterologous, and accordingly the rejection should be withdrawn.

In paragraph 28 of the Action, the Examiner stated the term "stringent" is relative and therefore renders claim 156 indefinite. "Stringent" is a common term in the art and is defined in many well known treatises such as Sambrook *et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratories* (New York, 1989) and Ausbel *et al. Current Protocols in Molecular Biology,* Green Publishers Inc. and Wiley and Sons, NY (1994). The specification defines stringent hybridization conditions at page 34, lines 23-26. In addition, a recent search of the U.S. Patent and Trademark Office Issued Patent Database identified more than 12000 issued patents that recite the term "stringent" in the claims. A portion of this search is attached herewith as Appendix B.

In view of the foregoing remarks, the rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

VIII. The Rejection Under 35 U.S.C. § 102(b) should be Withdrawn.

In paragraph 29 of the Action, the Examiner rejected claims 151-169 under 35 U.S.C. § 102(b) as being anticipated by WO 00/17369 (PCT Application No. PCT/US99/20881). As discussed in the telephonic interview and above, this rejection was in made error because the effective filing date for the present application is September 23, 1998. The publication date of WO 01/17369 is March 30, 2000 which is after the effective filing date of the present application.

In view of the foregoing remarks, the Applicants request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

CONCLUSION

In light of the forgoing amendment and remarks, the Applicants believe claims 155, 156 and 159-169 are in condition for allowance and early notice thereof is earnestly solicited.

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Respectfully submitted,

By _____

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